BIOG.

TWO ROSS-MANSON LETTERS.

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PREFATORY NOTE.

My early correspondence on malaria with Dr. Patrick Manson, Dr. Alphonse Laveran, Lord Lister and possibly some others, will probably be published shortly in full; but I think that those who are interested in the subject may like to see now the following copies of the two letters of August, 1897, to Manson, in which I recorded the finding of the malaria parasites in the tissues of two *Anopheles* mosquitoes. The next year I proved by the analogy of Culex mosquitoes fed on birds containing avian malaria that the cells found on August 20th and 21st 1897, were really derived from the malaria parasites of man, just as I conjectured in the following letters.

As I have often explained, I could not obtain at that time any literature in India on Indian mosquitoes; and I was obliged to invent the whole of the *technique* concerned for myself. It was these two observations which rendered possible all the immense amount of work on malaria and mosquitoes which has been done throughout malarious countries since those dates. I have added a few explanatory footnotes.

I am also taking the opportunity of appending an extract from the recent Presidential address delivered by Dr. G. Carmichael Low to the Royal Society of Tropical Medicine on October 18th last, because it is probably the best brief account ever published in English of my Indian work—a subject regarding which most inaccurate histories have appeared, and still continue to appear even after thirty years' exposition.

RONALD ROSS,

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Putney Heath, S.W. 15.

November 2nd, 1929.

THE LETTERS.

SECUNDERABAD,
August 22nd, 1897.

COPY.

DEAR DR. MANSON,

In my last I told you that I was going to abandon the brindled mosquitoes for a while, and attack some brown ones. Now prick up your ears because the hunt is up again. It may be a false scent, but it smells promising.

Unfortunately it turned out that my mosquitoes (brown)* were very few in number, but they bit well and kept well. I dissected the first ones without any result, but some were bad dissections, broken eggs, etc. On Friday, 20th, I had only two left. One was very carefully dissected (fourth day after being fed on crescents†). I noticed at once some cells in the stomach rather more distinct than the usual very delicate stomach cells. Altogether there were a dozen of these lying mainly towards the upper end of the organ. They varied from 12μ to 16μ in diameter and were full of stationary vacuoles. The outline was sharp but fine and not at all amœboid, the shape spherical or ovoid, the substance rather more solid than that of the neighbouring cells. There was no contractile vesicle ; but one or two of the cells seemed to be contained in some of the large gastric cells. Now I am so familiar with the mosquito's stomach that these bodies struck me at once, and you may imagine how much more struck I was when, on focussing carefully I found that they contained *pigment indistinguishable in colour, shape, etc., from that of the hœmamœba* !‡ It was black or dark brown (not blue, or yellow or greenish like the cell granules, debris, etc.), not refractive on up-focussing, consisting of little balls or rods, and sometimes oscillating rapidly within a small range in parts of the cells. This pigment was not however copious at all and the

* These turned out ultimately to be *Anopheles*, probably *A. stephensi*.

† That is, on human blood containing crescents.

‡ An old name for the malaria parasites now called *Plasmodia*.

granules did not shift their place in the cell appreciably; though I find on comparing drawings that they alter their position after 24 hours. In some cells there were pretty large clumps of pigment; in fact the latter was *exactly* and *in every detail* like the pigment of the hæmamœba.

Now what do you think of this? Well, I irrigated with formaline, sealed with glue and labelled for you. Examining next day, the cells, as I expected they would under formaline, showed up more clearly and could now be made out easily with a 1/6th inch. The pigment had clustered more into clumps. In fact apart from the pigment, the bodies looked parasitic, though they were not nearly so bright as the coccidia I sent you from Sigur.

On the 21st I killed my last brown mosquito (five days after being malariated) and rushed at the stomach. The very same bodies (!) only larger, more distinct and with a thicker perhaps double, outline (sometimes). There were 21 of them, again in the œsophageal half of the stomach. The largest ones were 20 μ, but some were only 12–14 μ. Pigment and vacuoles as before. Formaline, etc., again. I will send you the specimens when I can get some more (I want them now for comparison).

No more brown mosquitoes!

In their absence, I have taken a number of brindled* malariated mosquitoes which I had ready, and have examined them again to make sure that I had not previously overlooked the pigmented bodies. Not one in eight of them.

Hence we have provisionally:—

(1) The pigmented cells appear to exist in malariated brown mosquitoes but not in brindled ones.
(2) They are larger on the fifth than on the fourth day.
(3) They occupy only one part of the stomach.
(4) They become more distinct under formaline.
(5) They are sometimes intracellular (?)
(6) They have pigment exactly like that of the malaria parasite.

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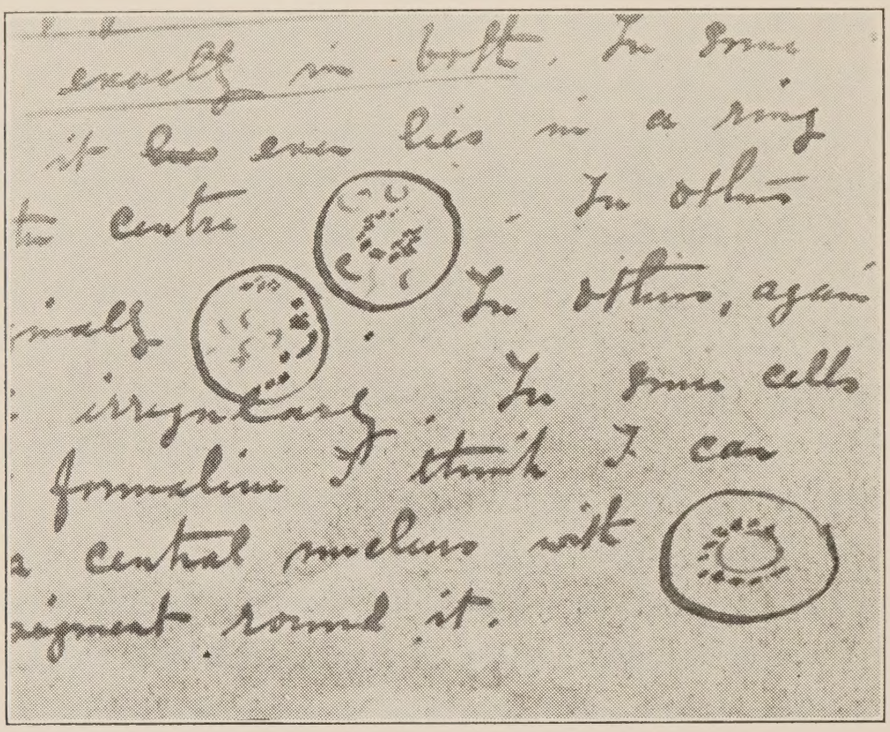
* *Stegomyia.*

The remarkable thing about them is undoubtedly the pigment. I have never seen this before in any mosquito (I have now examined hundreds—or a thousand). It always lies in the cells and is not scattered outside them or in any other cells. In short, it is as distinctive a feature of them as it is of the hæmamœba. *No other bodies but these two that I have ever seen contain such pigment*; *and it is the same exactly in both.* In some cells it even lies in a ring at the centre (*see* diagram). In others marginally (*see* diagram). In others, again quite irregularly. In some cells after formaline I think I can see a central nucleus with the pigment round it (*see* diagram).



Photograph of a portion of a letter, written by Ross to Manson, August 22nd, 1897, containing original drawings of malaria zygotes in mosquitoes as first seen.

Wait now. You will say at once (as I used to think) that the parasite in the mosquito cannot have pigment, because this is known to be derived from hæmoglobin, and the mosquito has no hæmoglobin. Has it not though ? Why its stomach is full of it, and these cells which lie in the wall of the stomach, perhaps almost touching its contents, could easily absorb unlimited hæmoglobin.* Anyway there's the pigment, just like what we see in our old friend.

* This hypothesis was unsound.

Only one difficulty remains—to get more brown mosquitoes. I may add that it is a filaria*-bearing species. One of my patients has very rare filariæ and I found one kicking in the *tissues* of a 24-hour mosquito.

I must first keep my mosquitoes alive for more than five days, by giving them a second feed, in order to see whether the pigmented cells develop spores. By their appearance on the fifth day I imagine sporulation will begin at about the seventh day.† If spores form, the parasitic nature of the cells is established and, taken together with the pigment, leads to an obvious inference.

Next I have to see whether unfed brown mosquitoes or the same fed on healthy blood do or do not possess these cells, and whether malariated ones always possess them.

All this is only a matter of a little work. Unfortunately I can't get any more of those brown devils.

Meantime the find of pigment is as encouraging as it is unexpected. It is of course quite unlikely that these cells are mere ordinary cells which have absorbed pigment granules from the stomach-contents by amœboid action. The cells are too few and their pigment too scattered and scarce—not like that of a pigmented spleen-cell for instance. Besides, why should they not exist in the brindled insects ?

August 23rd. No brown mosquitoes yet. Can doing [*sic*] nothing else but look at my pigmented cells. They keep beautifully in formaline. The pigment, though much more scanty in comparison to the size of the cell, is absolutely identical in characters with that of the hæmamœba. I have never seen anything like it before except in the hæmamœba. Wonder if I am really on it at last ! If not, what can these cells be ? Something very unusual.

5 p.m. Two brown mosquitoes caught in hospital ward,‡ a male and female, the latter containing one day's blood. No pigmented

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* Quite another parasite of man.

† I was right.

‡ Probably *Anopheles culicifacies*.

cells. These then appear to be not a normal feature even in brown mosquitoes.

Two points must be proved—(*a*) that the cells are parasites; (*b*) that they are malaria parasites. Please note, however, that owing to the presence of pigment, (*a*) will really almost involve (*b*). Hence, if I can find that the cells *sporulate*, the thing is *morally* certain, though formal proof of (*b*) will be required.

August 24th. No more brown mosquitoes bred from grubs; but I have caught 10*, 1 male, 7 unfed females, and 2 females whose stomachs and ova show that they were fed two and three days ago. In none of these have I found pigmented cells, though all were examined most carefully. It appears then that these cells are peculiar to malariated brown mosquitoes.

With kind regards,

Believe me,

Yours sincerely,

(Signed) R. ROSS.

SECUNDERABAD,
August 31*st*, 1897.

DEAR DR. MANSON,

Very many thanks for yours of the 11th. Will you kindly ask your publisher to send me a copy of your book with note of price. I will return cheque. Am glad you have got it off, and am anxious to read it. Please give Mrs. Manson my thanks and compliments for the copies of the very interesting articles. They must have cost her a great deal of trouble to copy, especially the accents. I must get a typewriter (for my wife) as soon as possible. I expect that the malaria flagellæ have an axial nucleus like the coccidial flagellæ described by Simond. Hence the reason why you cannot make out a nucleus—the whole thing almost is a nucleus (?)

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* Probably *Anopheles culicifacies*.

I am in despair about my specimens having gone bad, because now I dare not send you the two slides of pigmented cells in the mosquito, since they also have been mounted in formaline. I suppose it was the Red Sea, because my own specimens of coccidia and octospores are in perfect condition. I cannot understand how bacteria, however numerous, could have destroyed either of these which are hard resistant bodies. Are you quite sure that you have not overlooked them? The octospores are found among the abdominal scales; the coccidia in the stomach. For both use an oil immersion. My coccidia now look like worm eggs, very distinct; but the octospores may be mistaken for fat globules.

You will be dying to know about the new cells. I have had a maddening exasperating week owing to my not finding any more of those infernal brown mosquitoes; and at the end of this week I must go to Bangalore to see my wife and children. Is it not annoying?* I have had half a dozen men out hunting grubs and have obtained scores of hatches—all brindled or grey. The ones I caught in the ward turn out not to be exactly the right kind, though very closely allied, being whiter and more slender. I cannot find where even these come from, and those caught by hand won't bite, even at night. These kinds constitute evidently a separate family of mosquitoes characterised by having dappled wings and peculiar boat-shaped eggs. I will be on them in time.

I have examined crowds of other kinds for the pigmented cells, without result. I am now going methodically through a grey species with six dark grey bands on back and grey plain wings.† Will let you know result up to fourth day to-morrow.

Now to open my heart freely—I really believe the problem is solved, though I don't like to say so. I look at my cells daily; those of the fifth day have grown bigger than those of the fourth day; such bodies are not found normally among the elementary cells of the mosquito's stomach (which are alike in all species of

* I have got into terrible trouble for this remark, but the reader will grasp my inner meaning.

† *Culex fatigans.*

course) ; they have as yet been found only in malariated mosquitoes ; above all, they contain the characteristic pigment peculiar to the malaria bug. What are we to think : What do *you* think ? I fancy when you first read the word " pigment " you guessed what it was. Well now, I daren't send you these specimens for fear they spoil on the way. I will take them to Bangalore and show them all round. John Smyth is there, I think, and some other men who have got a little knowledge of the malaria bug. I'll make them write descriptions, which I will send with a short note of my own to the B.M.J. Then on returning here I will try and photograph the cells (if I haven't succeeded in finding them again). I think, after deliberation, that the find should be notified as soon as possible, as it may, for one cause or another, be weeks before I get on to the cells again, and in the meantime some lucky Italian or American, who has happened to hit off the right species of insect, may polish off the whole business. My note to the B.M.J. will contain descriptions of the mosquito and of the cells and will draw only such cautious references as we are as yet entitled to make. In reality—*pigment*—it is almost proof already ! What else can the thing be ? Mosquito cells don't contain pigment, or anything like it. I am not mistaken—it is *pigment*, absolute, unmistakable *pigment* ! I have hardly restrained myself from wiring " pigment " to you, but fear you would think that I had gone mad. Well, I know pigment by this time. *I am on it.*

September 1st.—The grey mosquitoes don't contain pigmented cells up to the fourth day. Several more batches of grubs yield only brindled mosquitoes. My crescent cases are nearly exhausted. Hence I must now defer study, until I return from leave. I think you will agree with me that I should not risk my two precious specimens until I have shown them and got some photos. Owing to the border war it is quite possible I may be sent on active service. Leslie has not troubled to reply to my letter. Nor have Sir W. Young, Maharajah of Dholput, Cleghorne, and a friend at Simla, to all of whom I wrote months or weeks ago. Funny people out here. I shall look out for brown mosquitoes at Bangalore and am

offering large rewards to my hospital servants here for them. There was no gregarine (except perhaps accidentally) in the specimens I sent you.

With kind regards,

Yours truly,
(Signed) R. ROSS.

Extract from Dr. G. Carmichael Low's Presidential address to the Royal Society of Tropical Medicine, October 18th, 1929.

*"In Bangalore in 1889 Ross had studied malaria, but failed to confirm Laveran's discovery of the malaria parasite. Manson now showed him the parasite and withal explained his famous mosquito-malaria hypothesis which had been born of and fostered by his pioneer work in Amoy in 1877 on the development of the embryos of *Filaria bancrofti* in the tissues of the mosquito. In 1894 the predominant opinion was that 'flagellation' of the malaria parasite signified, and was the product of, the parasite's death and disintegration. Manson taught the contrary: "Since the flagella appear only when malaria blood gets outside the body," he said, "their purpose must be to continue the life of the parasite in the outer world . . . for the purpose of infecting mosquitoes which suck the blood of patients." This was a chain of reasoning from which Ross found it impossible to escape; and in the upshot, on returning to India in 1895 he, for his part, began those researches which eventually justified the hypothesis that malaria was transmitted by mosquitoes. But before this historic achievement MacCallum, in 1897, settled all controversy about the exact nature of the 'flagella' by showing that they were microgametes. On August 20th and 21st, 1897, Ross, in Secunderabad, made an important discovery. In the stomach of two 'spotted-winged mosquitoes,' bred from larvæ and fed on a patient with malaria crescents in the blood, he found

* Reprinted from the 'Lancet,' November 2nd, 1929, p. 927.

certain cells containing pigment granules indistinguishable from those seen in malaria parasites ; and a month later he found like cells in another species of anopheles—also bred from larvæ and fed on malarial blood. This shining discovery Ross reported promptly to his chief in the Madras Presidency ; and now, with the solution of the great problem in his grasp, he was given urgent orders to proceed at once to Rajputana where the dry cold weather put an end to mosquito work. At this juncture Manson interceded with the India Office in London, with result that in January, 1898, Ross was placed on special duty for six months to continue his malaria research. He arrives in Calcutta in the following February, but now armed with MacCallum and Opie's proof that the crescents were sexual forms and not special 'sporulating' ones. Human malaria was scarce in Calcutta, so, acting on Manson's suggestion, Ross turned to the malaria of birds, and here found material in plenty. In March he had tracked down the species of mosquito capable of carrying the malaria parasite of birds, and within a few more weeks had traced step by step the cycle of the parasite's development in this mosquito. In July, 1898, he telegraphed to Manson, who announced the discovery at the British Medical Association meeting in Edinburgh, at the end of that month. But the 'mugwumps' had not finished with Ross ; again and quickly he was forced to discontinue malaria work. He was sent to Assam to investigate kala-azar, and thus, said Dr. Low, it fell to Grassi, Bignami and Bastianelli, in Rome, to verify the great discovery for human malaria. This would not have been done at the time but for Ross's work—the Italian researches followed his, and were not independent of them."

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